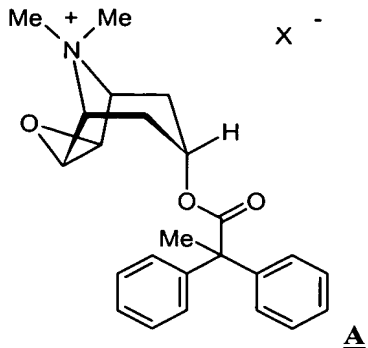
Patent Claims

1) A Pharmaceutical composition comprising one or more anticholinergics of formula **A**



A

wherein

X^- denotes an anion (counter-ion), preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methansulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate

combined with one or more p38 kinase inhibitors (**B**), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.

2) The Pharmaceutical composition according to claim 1, wherein the active substances **A** and **B** are present either together in a single formulation or in two separate formulations.

3) The Pharmaceutical composition according to claim 2, wherein for **A** X^- is selected from among chloride, bromide, methansulphonate and p-toluenesulphonate.

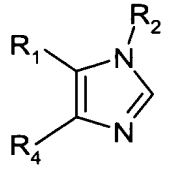
4) The Pharmaceutical composition according to claim 3, characterised in that in **A** X^- denotes bromide.

5) The Pharmaceutical composition according to claim 4, wherein the p38 kinase inhibitor **B** is selected from the group of compounds disclosed in US Patents 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, US 6,277,989, US 6,340,685, and US 5,716,955 and PCT applications WO 92/12154, WO 94/19350, WO 95/09853, WO 95/09851, WO 95/09847, WO 95/09852, WO 97/25048, WO 97/25047, WO 97/33883, WO 97/35856, WO 97/35855, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/25619, WO 98/06715, WO 98/07425, WO 98/28292, WO 98/56377, WO 98/07966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52559, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098, WO 98/47892, WO 98/47899, WO 98/50356, WO 98/32733, WO 99/58523, WO 99/01452, WO 99/01131, WO 99/01130, WO 99/01136, WO 99/17776, WO 99/32121, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 99/00357, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 99/15164, WO 99/32110, WO 99/32111, WO 99/32463, WO 99/64400, WO 99/43680, WO 99/17204, WO 99/25717, WO 99/50238, WO 99/61437, WO 99/61440, WO 00/26209, WO 00/18738, WO 00/17175, WO 00/20402, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/35911, WO 00/39116, WO 00/43384, WO 00/41698, WO 00/69848, WO 00/26209, WO 00/63204, WO 00/07985, WO 00/59904, WO 00/71535, WO 00/10563, WO 00/25791, WO 00/55152, WO 00/55139, WO 00/17204, WO 00/36096, WO 00/55120, WO 00/55153, WO 00/56738, WO 01/21591, WO 01/29041, WO 01/29042, WO 01/62731, WO 01/05744, WO 01/05745, WO 01/05746, WO 01/05749, WO 01/05751, WO 01/27315, WO 01/42189, WO 01/00208, WO 01/42241, WO 01/34605, WO 01/47897, WO

01/64676, WO 01/37837, WO 01/38312, WO 01/38313, WO 01/36403, WO 01/38314, WO 01/47921, WO 01/27089, DE 19842833, and JP 2000 86657.

6) The Pharmaceutical composition according to claim 5, wherein the p38 kinase inhibitor **B** is selected from the group of compounds disclosed in US 6,277,989, US 6,340,685, WO 00/12074, WO 00/12497, WO 00/59904, WO 00/71535, WO 01/64676, WO 99/61426, WO 00/10563, WO 00/25791, WO 01/37837, WO 01/38312, WO 01/38313, WO 01/38314, WO 01/47921, WO 99/61437, WO 99/61440, WO 00/17175, WO 00/17204, WO 00/36096, WO 98/27098, WO 99/00357, WO 99/58502, WO 99/64400, WO 99/01131, WO 00/43384, WO 00/55152, WO 00/55139, and WO 01/36403.

7) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **1**



1

wherein

R_1 is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolinyl, or quinazolin-4-yl ring, which ring is substituted with Y-R_a and optionally with an additional independent substituent selected from C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} akylthio, C_{1-4} aklylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15}, $N(R_{10})C(O)R_b$ or NHR_a;

Y is oxygen or sulfur;

R_4 is phenyl, naphth-1-yl or naphth—yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and

which, for a 4-phenyl, 4naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $C(Z)NR_7R_{17}$, $C(Z)OR_{16}$, $(CR_{10}R_{20})_vCOR_{12}$, SR_5, SOR_5, OR_{12}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $ZC(Z)R_{12}$, $NR_{10}C(Z)R_{16}$, or $(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $C(Z)NR_{13}R_{14}$, $C(Z)OR_3$, $(CR_{10}R_{20})_{m"}COR_3$, $S(O)_mR_3$, OR_3, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $(CR_{10}R_{20})_{m"}R_{10}C(Z)R_3$, $NR_{10}S(O)_{m'}R_8$, $NR_{10}S(O)_{m'}NR_7R_{17}$, $ZC(Z)R_3$ or $(CR_{10}R_{20})_{m"}NR_{13}R_{14}$;

Z is oxygen or sulfur;

n is an integer having a value of 1 to 10;

m is 0, or integer 1 or 2;

m' is an integer having a value of 1 or 2;

m" is 0, or an integer having a value of 1 to 5;

v is 0, or an integer having a value of 1 to 2;

R_2 is –C(H) (A) (R_{22});

A is optionally substituted aryl, heterocyclyl, or heteroaryl ring, or A is substituted C_{1-10} alkyl;

R_{22} is an optionally substituted C_{1-10} alkyl;

R_a is aryl, arylC_{1-6} alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6}alkyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl, wherein each of these moieties may be optionally substituted;

R_3 is heterocyclyl, heterocyclyl C_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties SR_5 being $SNR_7R_{17}$and SOR_5 being SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclyl, aryl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, C(Z) R_{11} or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl, wherein these moieties may be optionally substituted;

R_{12} is hydrogen or R_{16};

R_{13} an R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted arylC_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

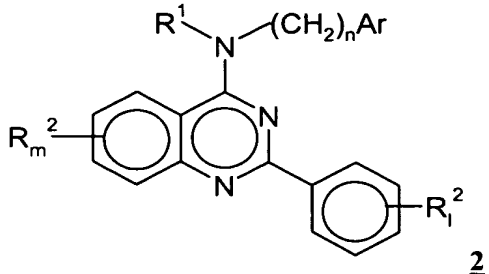
R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$ alkyl, heterocyclyl, heterocyclyl- C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$ alkyl;

or a pharmaceutically acceptable salt thereof.

8) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **2**



2

wherein

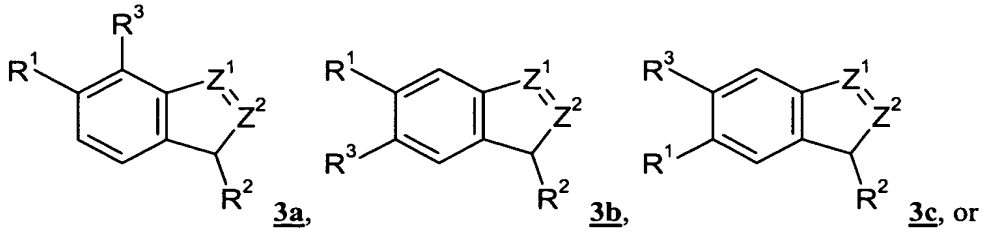
R^1 is H, alkyl(1-6C) or arylalkyl optionally substituted on the aryl group with 1-3 substituents independently selected from alkyl (1-6C), halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, $-SO_2NR_2$, CN, CF_3, and NO_2, wherein each R is independently H or lower alkyl (1-4C);

each R^2 is independently alkyl (1-6C), halo, OR, SR, OOCR, NROCR, COOR, RCO, $CONR_2$, SO_2NR_2, CN, CF_3 or NO_2, wherein each R is independently H or lower alkyl (1-4C);

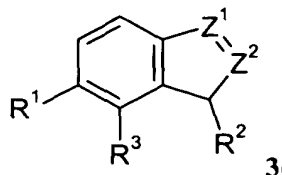
each of l, m, and n is independently 0, 1 or 2; and

Ar is phenyl, 2-, 3- or 4-pyridyl, indolyl, 2- or 4-pyrimidyl, or benzimidazolyl, each optionally substituted with optionally substituted alkyl, alkenyl, alkynyl, aryl, N-aryl, NH-aroyl, halo, OR, NR_2, SR, -OOCR, -NROCR, RCO, -COOR, $-CONR_2$, SO_2NR_2, CN, CF_3, or NO_2, wherein each R is independently H or alkyl (1-4C), or the pharmaceutically acceptable salts thereof.

9) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **3a**, **3b**, **3c**, or **3d**



3a, **3b**, **3c**, or



3d

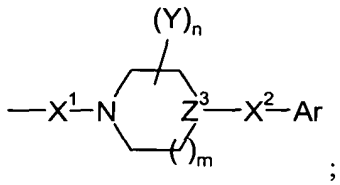
and the pharmaceutically acceptable salts thereof,

wherein each of Z^1 and Z^2 is independently CR^4 or N;

where each R^4 is independently selected from H and alkyl(1-6C);

wherein said alkyl optionally includes one or more heteroatoms selected from O, S and N, and wherein said alkyl is optionally substituted by one or more substituents selected from halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, CN, =O, a 5 or 6 membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a 6-membered aromatic ring optionally containing 1-2 N heteroatoms, wherein R in the foregoing optional substituents is H or alkyl (1-6C);

R^1 is



;

wherein

X^1 is CO, SO, CHOH or SO_2 ;

m is 1;

Y is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

n is 0, 1 or 2;

Z^3 is N;

X^2 is CH or CH_2 ; and

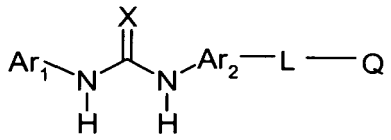
Ar consists of one or two phenyl moieties directly coupled to X^2, said one or two phenyl moieties being optionally substituted by a substituent selected from halo, nitro, alkyl (1-6C), alkenyl (1-6C), CN, CF_3, RCO, COOR, $CONR_2$, NR_2, OR, SR, OOCR,

NROCR, (wherein R in the foregoing is H or 1-6C alkyl), and phenyl, itself optionally substituted by the foregoing substituents;

R^2 is selected from H, and alkyl (1-6C);
wherein said alkyl optionally includes one or more heteroatoms which are selected from O, S and N, and wherein said alkyl is optionally substituted by one or more substituents selected from halo, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, NROCR, (where R in the foregoing is H or 1-6C alkyl) CN, =O, a 5 or 6 membered saturated carbocyclic ring or heterocyclic ring containing 1-2 N, and a 6-membered aromatic ring optionally containing 1-2 N heteroatoms;

R^3 is H, halo, NO_2, alkyl (1-6C), alkenyl (1-6C), CN, OR, SR, NR_2, RCO, COOR, $CONR_2$, OOCR, or NROCR where R is H or alkyl (1-6C).

10) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **4**



4

wherein

Ar_1 is a heterocyclic group selected from the group consisting of pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;
and wherein Ar_1 may be substituted by one or more R_1,R_2 or R_3;

Ar_2 is phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R_2 groups;

L, a linking group, is a
C_{1-10} saturated or unsaturated branched or unbranched carbon chain;

wherein one or more methylene groups are optionally independently replaced by O,N or S; and

wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl which may be substituted by one or more halogen atoms;

Q is selected from the group consisting of:

a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, imidazole, benzimidazole, furan, thiophene, pyran, naphthyridine, oxazo[4,5-*b*]pyridine and imidazo[4,5-*b*]pyridine, which are optionally substituted with one to three groups selected from the group consisting of halogen,

C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$ and phenylamino wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, piperidine, piperidinone, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino-C_{1-3} alkyl, phenylamino-C_{1-3} alkyl and C_{1-3} alkoxy-C_{1-3} alkyl;

c) C_{1-6} alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C_{1-3} alkyl and C_{1-5} alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_r$, phenyl-$S(O)_t$, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino;

R_1 is selected from the group consisting of:

a) C_{3-10} branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and di(C_{1-3})alkylaminocarbonyl;

b) C_{3-7} cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which may optionally be partially or fully halogenated and which may optionally be substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, CHOH, >C=O, >C=S and NH;

c) C_{3-10} branched alkenyl which may optionally be partially or fully halogenated, and which is optionally substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$, mono- or di(C_{1-3})alkylaminocarbonyl;

d) C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl,

wherein such cycloalkenyl group may optionally be substituted with one to three C_{1-3} alkyl groups;

e) cyano; and,

f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of:

a C_{1-6} branched or unbranched alkyl which may optionally be partially or fully halogenated, acetyl, aroyl, C_{1-4} branched or unbranched alkoxy, which may optionally be partially or fully halogenated, halogen, methoxycarbonyl and phenylsulfonyl;

R_3 is selected from the group consisting of:

a) a phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl; wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heterocycle selected from the group hereinabove described, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5}

alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4-C_{1-5} alkyl, R_5-C_{1-5} alkoxy, R_6–C(O)-C_{1-5} alkyl and R_7-C_{1-5} alkyl(R_8)N;

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} alkyl-OC(O),

C_{1-5} alkyl-C(O)-C_{1-4} branched or unbranched alkyl, an amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_9-C_{1-5} alkyl, R_{10}-C_{1-5} alkoxy, R_{11}–C(O)-C_{1-5} alkyl, and R_{12}-C_{1-5} alkyl(R_{13})N;

c) cycloalkyl selected from the group consisting of cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which the cycloalkyl may optionally be partially or fully halogenated and which may optionally be substituted with one to three

C_{1-3} alkyl groups;

d) C_{5-7} cycloalkenyl, selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group may optionally be substituted with one to three C_{1-3} alkyl groups; and

e) acetyl, aroyl, alkoxycarbonylalkyl or phenylsulfonyl;

f) C_{1-6} branched or unbranched alkyl which may optionally be partially or fully halogenated;

or R_1 and R_2 taken together may optionally form a fused phenyl or pyridinyl ring,

and wherein each R_8, R_{13} is independently selected from the group consisting of:

hydrogen and C_{1-4} branched or unbranched alkyl which may optionally be partially or fully halogenated;

each R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of:

morpholine, piperidine, piperazine, imidazole and tetrazole;

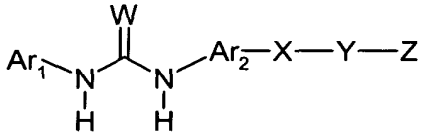
m = 0, 1, 2;

r = 0, 1, 2;

t = 0, 1, 2;

X = O or S and physiologically acceptable acids or salts thereof.

11) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **5**



5

wherein:

Ar_1 is selected from the group consisting of:
pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;
wherein Ar_1 may be substituted by one or more R_1, R_2 or R_3;

Ar_2 is:
phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl or indole each being optionally substituted with zero to three R_2 groups;

X is:

a) a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with 0-2 oxo groups or 0-3 C_{1-4} branched or unbranched alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains;

b) phenyl, furan, thiophene, pyrrole, imidazolyl, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide, piperdine, piperazine or pyrazine each being optionally independently substituted with 0-3 C_{1-4} branched or unbranched alkyl, C_{1-4}alkoxy, hydroxy, nitrile, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$, or halogen;

Y is:
a bond or a C_{1-4} saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, S(O), $S(O)_2$ or S and wherein Y is optionally independently substituted with 0-2 oxo groups and one or more C_{1-4} branched or unbranched alkyl which may be substituted by one or more halogen atoms;

Z is:

a) phenyl, pyridine, pyrimidine, pyridazine, imidazole, furan, thiophene, pyran, which are optionally substituted with one to three groups consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$, COOH and phenylamino wherein the phenyl ring is optionally

substituted with one to two groups consisting of halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine sulfoxide, piperidine, piperidinone, piperazine, tetrahydropyrimidone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide or tetramethylene sulfone which are optionally substituted with one to three groups consisting of nitrile, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, mono- or di-(C_{1-3} alkyl)amino-C_{1-3} alkyl, phenylamino-C_{1-3} alkyl and C_{1-3} alkoxy-C_{1-3} alkyl;

c) C_{1-6} alkoxy, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C_{1-3} alkyl, C_{1-5} alkoxyalkyl, pyridinyl-C_{1-3} alkyl, imidazolyl-C_{1-3} alkyl, tetrahydrofuranyl-C_{1-3} alkyl, phenylamino, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$, and phenyl-$S(O)_m$, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino;

R_1 is :

a) C_{3-10} branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described in this paragraph, and being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, nitrile, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and di(C_{1-3})alkylaminocarbonyl;

b) C_{3-7} cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl each being optionally be partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S, CHOH, >C=O, >C=S and NH;

c) C_{3-10} branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, nitrile, C_{1-3} alkoxy which is optionally partially or fully halogenated, $NH_2C(O)$ and mono- or di(C_{1-3})alkylaminocarbonyl;

d) a C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) nitrile; or

f) C_{1-6} branched or unbranched alkoxycarbonyl, C_{1-6} branched or unbranched alkylaminocarbonyl, C_{1-6} branched or unbranched alkylcarbonylamino-C_{1-3}-alkyl;

R_2 is:

a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C_{1-4} branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

R_3 is:

a) phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl, wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of phenyl, naphthyl, heterocycle selected from the group hereinabove described in this paragraph, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halogen, hydroxy, nitrile, C_{1-3} alkyloxy which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4 -C_{1-5} alkyl, R_5 -C_{1-5} alkoxy, R_6–C(O)-C_{1-5} alkyl and R_7 -C_{1-5} alkyl(R_8)N, carboxy-mono- or di-(C_{1-5})-alkyl-amino;

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting

of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halogen, nitrile, C_{1-3} alkoxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} alkyl-OC(O), C_{1-5} alkyl-C(O)-C_{1-4} branched or unbranched alkyl, an amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_9 -C_{1-5} alkyl, R_{10} -C_{1-5} alkoxy, R_{11} –C(O)-C_{1-5} alkyl, and R_{12} -C_{1-5} alkyl(R_{13})N;

c) cycloalkyl selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

d) C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) acetyl, aroyl, alkoxycarbonylalkyl or phenylsulfonyl; or

f) C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated;

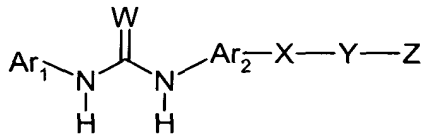
or R_1 and R_2 taken together may optionally form a fused phenyl or pyridinyl ring;

each R_8 and R_{13} is independently selected from the group consisting of:
hydrogen and C_{1-4} branched or unbranched alkyl optionally be partially or fully halogenated;

each R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;

m is 0, 1 or 2;
W is O or S and pharmaceutically acceptable derivatives thereof.

12) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **5a**



5a

wherein:

Ar_1 is:
pyrrole, pyrrolidine, pyrazole, imidazole, oxazole, thiazole, furan and thiophene;
wherein Ar_1 is optionally substituted by one or more R_1, R_2 or R_3;

Ar_2 is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, tetrahydroquinoline, tetrahydroisoquinoline, benzimidazole, benzofuran, indanyl, indenyl and indole each being optionally substituted with zero to three R_2 groups;

X is:

a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains each being branched or unbranched;

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, tetrahydropyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C_{1-4} alkyl, C_{1-4}alkoxy, hydroxy, nitrile, amino, mono- or di-(C_{1-3} alkyl)amino, mono- or di-(C_{1-3} alkylamino)carbonyl, $NH_2C(O)$, C_{1-6} alkyl-$S(O)_m$ or halogen;

Y is:

a bond or a C_{1-4} saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or $S(O)_m$ and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl, hydroxy or one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms;

Z is:

aryl, indanyl, heteroaryl selected from benzimidazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl, heterocycle selected from piperazinyl, tetrahydropyrimidonyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl,

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl,

each of the aforementioned Z are optionally substituted with one to three halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-6} alkoxycarbonyl, aroyl, heteroaroyl, heterocycleC_{1-3}acyl wherein the heteroaryl and heterocycle are as defined hereinabove in this paragraph, C_{1-3}acyl, oxo, hydroxy, pyridinyl-C_{1-3} alkyl, imidazolyl-C_{1-3} alkyl, tetrahydrofuranyl-C_{1-3} alkyl, nitrile-C_{1-3} alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, amino-$S(O)_m$, C_{1-6} alkyl-$S(O)_m$ or phenyl-$S(O)_m$ wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy, halogen or mono- or di-(C_{1-3} alkyl)amino;

or Z is optionally substituted with one to three amino, aminocarbonyl or amino-C_{1-3} alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC_{1-6}alkyl, C_{1-3}alkyl, arylC_{0-3}alkyl, C_{1-5} alkoxyC_{1-3} alkyl, C_{1-5} alkoxy, aroyl, C_{1-3}acyl, C_{1-3}alkyl-$S(O)_m$- or arylC_{0-3}alkyl-$S(O)_m$- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino;

or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

or Z is hydroxy, hydroxyC_{1-3}alkyl, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C_{1-6}alkyl, aminoC_{1-6}alkyl, arylC_{0-3}alkyl, C_{1-5} alkoxyC_{1-3} alkyl, C_{1-5} alkoxy, aroyl, C_{1-3}acyl, C_{1-3}alkyl-$S(O)_m$- , arylC_{0-3}alkyl-$S(O)_m$- , nitrileC_{1-4}alkyl or C_{1-3}alkoxyC_{1-3}alkyl, each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkoxyheteroarylC_{0-3}alkyl, heteroarylC_{0-3}alkyl or heterocycyleC_{0-3}alkyl wherein the heteroaryl and heterocycle is hereinabove described in this paragraph,

or Z is C_{1-6}alkyl branched or unbranched, C_{1-6}alkoxy, C_{1-3}acylamino, nitrileC_{1-4}alkyl, C_{1-6} alkyl-$S(O)_m$, and phenyl-$S(O)_m$, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino;

R_1 is :

a) C_{1-10} branched or unbranched alkyl optionally partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle, selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, nitrile, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$ and di(C_{1-3})alkylaminocarbonyl;

b) C_{3-7} cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, each optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from the group consisting of O, S, CHOH, >C=O, >C=S and NH;

c) C_{3-10} branched alkenyl optionally partially or fully halogenated and optionally substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from the group consisting of halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or

fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, nitrile, C_{1-3} alkoxy which is optionally partially or fully halogenated, $NH_2C(O)$ and mono- or di(C_{1-3})alkylaminocarbonyl;

d) a C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) nitrile; or

f) C_{1-6} branched or unbranched alkoxycarbonyl, C_{1-6} branched or unbranched alkylaminocarbonyl, C_{1-6} branched or unbranched alkylcarbonylamino-C_{1-3}-alkyl;

R_2 is:

a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated and optionally substituted with nitrile,

or R_2 is acetyl, aroyl, C_{1-4} branched or unbranched alkoxy optionally partially or fully halogenated, halogen, methoxycarbonyl or phenylsulfonyl;

R_3 is:

a) phenyl, naphthyl or heterocyclic group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl, wherein such phenyl, naphthyl or heterocyclic group is optionally substituted with one to five groups selected from the group consisting of a phenyl, naphthyl, heterocycle selected from the group hereinabove described in this paragraph, C_{1-6} branched or unbranched alkyl which is optionally partially

or fully halogenated, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl, bicycloheptyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halogen, hydroxy, oxo, nitrile, C_{1-3} alkoxy optionally partially or fully halogenated,

C_{1-3} alkoxyC_{1-5}alkyl, C_{1-3}thioalkyl, C_{1-3}thioalkylC_{1-5}alkyl, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described in this paragraph, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3})alkylamino-$S(O)_2$, R_4 -C_{1-5} alkyl, R_5 -C_{1-5} alkoxy, R_6 –C(O)-C_{1-5} alkyl and R_7 -C_{1-5} alkyl(R_8)N, carboxy-mono- or di-(C_{1-5})-alkyl-amino;

b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from the group consisting of cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from the group consisting of phenyl, naphthyl and heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halogen, nitrile, C_{1-3} alkoxy which is optionally partially or fully

halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heterocyclylamino wherein the heterocyclyl moiety is selected from the group hereinabove described, $NH_2C(O)$, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} alkyl-OC(O), C_{1-5} alkyl-C(O)-C_{1-4} branched or unbranched alkyl, an amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_9 -C_{1-5} alkyl, R_{10} -C_{1-5} alkoxy, R_{11} –C(O)-C_{1-5} alkyl and R_{12} -C_{1-5} alkyl(R_{13})N;

c) cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentyl, bicyclohexyl and bicycloheptyl, wherein the cycloalkyl is optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups;

d) C_{5-7} cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) acetyl, aroyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl or phenylsulfonyl; or

f) C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated;

or R_1 and R_2 taken together optionally form a fused phenyl or pyridinyl ring;

each R_8 and R_{13} is independently selected from the group consisting of: hydrogen and C_{1-4} branched or unbranched alkyl optionally partially or fully halogenated;

each R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11} and R_{12} is independently selected from the group consisting of morpholine, piperidine, piperazine, imidazole and tetrazole;

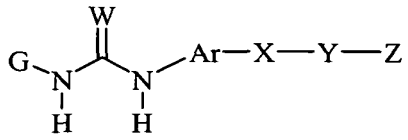
m is 0, 1 or 2;

W is O or S;

wherein X is directly attached to one or two -Y-Z, and

pharmaceutically acceptable derivatives thereof.

13) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula **6**



6

wherein:

G is :

an aromatic C_{6-10} carbocycle or a nonaromatic C_{3-10} carbocycle saturated or unsaturated;

a 6-10 membered heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 5-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from O, N and S;

wherein G is substituted by one or more R_1, R_2 or R_3;

Ar is:

phenyl, naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indolinyl, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R_4 or R_5;

X is:

a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains;

phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl;

Y is:

a bond or a C_{1-4} saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, N, or $S(O)_m$ and wherein Y is optionally independently substituted with one to two oxo groups, phenyl or one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms;

Z is:

phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, pyranyl each being optionally substituted with one to three halogen, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$, CN, $CONH_2$, COOH or phenylamino wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, piperazinyl, tetrahydropyrimidonyl, cyclohexanonyl, cyclohexanolyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfide, tetramethylene sulfoxidyl or tetramethylene sulfonyl each being optionally substituted with one to three nitrile, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, amino, mono- or di-(C_{1-3} alkyl)amino-C_{1-3} alkyl, $CONH_2$, phenylamino-C_{1-3} alkyl or C_{1-3} alkoxy-C_{1-3} alkyl;

halogen, C_{1-4} alkyl, nitrile, amino, hydroxy, C_{1-6} alkoxy, $NH_2C(O)$, mono- or di(C_{1-3}alkyl) aminocarbonyl, mono- or di(C_{1-6}alkyl)amino, secondary or tertiary amine wherein the amino nitrogen is covalently bonded to C_{1-3} alkyl or C_{1-5} alkoxyalkyl,

pyridinyl-C_{1-3} alkyl, imidazolyl-C_{1-3} alkyl, tetrahydrofuranyl-C_{1-3} alkyl, nitrile-C_{1-3} alkyl, carboxamide-C_{1-3} alkyl, phenyl, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$, or phenyl-$S(O)_m$, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy, halogen or mono- or di-(C_{1-3} alkyl)amino;

C_{1-6} alkyl-$S(O)_m$, and phenyl-$S(O)_m$, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino;

each R_1 is independently:

C_{1-10} alkyl optionally be partially or fully halogenated, and optionally substituted with one to three C_{3-10} cycloalkanyl, hydroxy, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to five groups selected from halogen, C_{1-6} alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkanyl, C_{5-8} cycloalkenyl, hydroxy, nitrile, C_{1-3} alkoxy which is optionally partially or fully halogenated or $NH_2C(O)$, mono- or di(C_{1-3}alkyl)amino, and mono- or di(C_{1-3}alkyl)aminocarbonyl;

cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups optionally partially or fully halogenated, CN, hydroxyC_{1-3}alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, $S(O)_m$, CHOH, >C=O, >C=S or NH;

phenyloxy or benzyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups optionally partially or fully halogenated, CN, hydroxyC_{1-3}alkyl or aryl; or an analog of such cycloaryl group wherein one to two ring methyne groups are independently replaced by N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups optionally partially or fully halogenated, CN, hydroxyC_{1-3}alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, $S(O)_m$, CHOH, >C=O, >C=S or NH;

C_{3-10} branched or unbranced alkenyl each being optionally partially or fully halogenated, and optionally be substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned being substituted with zero to five halogen, C_{1-6} alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$, mono- or di(C_{1-3}alkyl)aminocarbonyl; the C_{3-10} branched or unbranced alkenyl being optionally interrupted by one or more heteroatoms chosen from O, N and $S(O)_m$;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

nitrile, halogen;

methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

silyl containing three C_{1-4} alkyl groups optionally partially or fully halogenated;

C_{3-6} alkynyl branched or unbranched carbon chain optionally partially or fully

halogenated, wherein one or more methylene groups are optionally replaced by O, NH or $S(O)_m$ and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrrolidinyl, pyrrolyl, one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C_{1-3}alkyl)amino optionally substituted by one or more halogen atoms;

each R_2, R_4, and R_5 is

a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C_{1-4} branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, nitrile, methoxycarbonyl, C_{1-3} alkyl-$S(O)_m$ optionally partially or fully halogenated, or phenylsulfonyl;

C_{1-6} alkoxy, hydroxy, amino, or mono- or di-(C_{1-4} alkyl)amino, nitrile, halogen;

OR_6;

nitro; or

mono- or di-(C_{1-4} alkyl)amino-$S(O)_2$ optionally partially or fully halogenated, or H_2NSO_2;

each R_3 is independently:

phenyl, naphthyl, morpholinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazoyl, triazolyl, tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl or indazolyl, each of the aforementioned is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C_{1-6} branched

or unbranched alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halogen, hydroxy, oxo, nitrile, C_{1-3} alkyloxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocyclicoxy wherein the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3}alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as hereinabove described in this paragraph, $NH_2C(O)$, a mono- or di-(C_{1-3}alkyl) aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3}alkyl)amino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3}alkyl)amino-$S(O)_2$, R_7-C_{1-5} alkyl, R_8-C_{1-5} alkoxy, R_9-C(O)-C_{1-5} alkyl, R_{10}-C_{1-5} alkyl(R_{11})N, carboxy-mono- or di-(C_{1-5}alkyl)-amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl, cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl, cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl, cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl, cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl, cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl, cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl, cyclohexanoimidazolyl, cyclopentanothienyl and cyclohexanothienyl; wherein the fused aryl or fused heteroaryl ring is independently substituted with zero to three phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C_{1-6} alkyl which is optionally partially or fully halogenated, halogen, nitrile, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocyclicoxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3}alkyl)amino,

phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, $NH_2C(O)$, mono- or di-(C_{1-3}alkyl)aminocarbonyl, C_{1-4} alkyl-OC(O), C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_{12}-C_{1-5} alkyl, R_{13}-C_{1-5} alkoxy, R_{14}-C(O)-C_{1-5} alkyl or R_{15}-C_{1-5} alkyl(R_{16})N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C_{1-3} alkyl groups;

C_{1-4} alkyl-phenyl-C(O)-C_{1-4} alkyl-, C_{1-4} alkyl-C(O)-C_{1-4} alkyl- or C_{1-4} alkyl-phenyl-$S(O)_m$-C_{1-4} alkyl-;

C_{1-6} alkyl or C_{1-6} branched or unbranched alkoxy each of which is optionally partially or fully halogenated or optionally substituted with R_{17};

OR_{18} or C_{1-6} alkyl optionally substituted with OR_{18};

amino or mono- or di-(C_{1-5}alkyl)amino optionally substituted with R_{19};

$R_{20}C(O)N(R_{21})$-, $R_{22}O$- or $R_{23}R_{24}NC(O)$-; $R_{26}(CH_2)_mC(O)N(R_{21})$- or $R_{26}C(O)(CH_2)_mN(R_{21})$-;

C_{2-6}alkenyl substituted by $R_{23}R_{24}NC(O)$-;

C_{2-6} alkynyl branched or unbranched carbon chain, optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, $S(O)_m$ and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrroldinyl, pyrrolyl, morpholinyl, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C_{1-4} alkyl)amino optionally substituted by one or more halogen atoms; or

aroyl;

R_6 is a:

C_{1-4} alkyl optionally partially or fully halogenated and optionally substituted with R_{26};

each R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}, R_{15}, R_{17}, R_{19}, R_{25} and R_{26} is independently: nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl, amino or mono- or di-(C_{1-4}alkyl)amino optionally partially or fully halogenated;

each R_{11} and R_{16} is independently:

hydrogen or C_{1-4} alkyl optionally partially or fully halogenated;

R_{18} is independently:

hydrogen or a C_{1-4} alkyl optionally independently substituted with oxo or R_{25};

R_{20} is independently:

C_{1-10} alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

R_{21} is independently:

hydrogen or C_{1-3} alkyl optionally partially or fully halogenated;

each R_{22}, R_{23} and R_{24} is independently:

hydrogen, C_{1-6} alkyl optionally partially or fully halogenated, said C_{1-6} alkyl is optionally interrupted by one or more O, N or S, said C_{1-6} alkyl also being independently optionally substituted by mono- or di-(C_{1-3}alkyl)aminocarbonyl, phenyl, pyridinyl, amino or mono- or di-(C_{1-4}alkyl)amino each of which is optionally partially or fully halogenated and optionally substituted with mono- or di-(C_{1-3}alkyl)amino;

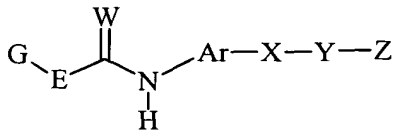
or R_{23} and R_{24} taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;

W is O or S and

pharmaceutically acceptable derivatives thereof.

14) The Pharmaceutical composition according to claim 6, wherein the p38 kinase inhibitor **B** is a compound of formula 7



7

wherein:

E is carbon or a heteroatom group chosen from -O-, -NH- and -S-;

G is :

an aromatic C_{6-10} carbocycle or a nonaromatic C_{3-10}carbocycle saturated or unsaturated;

a 6-14 membered monocyclic, bicyclic or tricyclic heteroaryl containing 1 or more heteroatoms chosen from O, N and S;

a 6-8 membered monocyclic heterocycle containing one or more heteroatoms chosen from O, N and S;

or

an 8-11 membered bicyclic heterocycle, containing one or more heteroatoms chosen from O, N and S;

wherein G is optionally substituted by one or more R_1, R_2 or R_3;

Ar is:

phenyl, naphthyl, quinolinyl, isoquinolinyl, tetrahydronaphthyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, indolinyl, benzothienyl, dihydrobenzothienyl, indanyl, indenyl or indolyl each being optionally substituted by one or more R_4 or R_5;

X is:

a C_{5-8} cycloalkyl or cycloalkenyl optionally substituted with one to two oxo groups or one to three C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} alkylamino chains each being branched or unbranched;

aryl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyridinonyl, dihydropyridinonyl, maleimidyl, dihydromaleimidyl, piperdinyl, benzimidazole, 3H-imidazo[4,5-b]pyridine, piperazinyl, pyridazinyl or pyrazinyl; each being optionally independently substituted with one to three C_{1-4} alkyl, C_{1-4}alkoxy, hydroxy, nitrile, amino, mono- or di-(C_{1-3} alkyl)amino, mono- or di-(C_{1-3} alkylamino)carbonyl, $NH_2C(O)$, C_{1-6} alkyl-$S(O)_m$ or halogen;

Y is:

a bond or a C_{1-4} saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more C atoms are optionally replaced by O, N, or $S(O)_m$ and wherein Y is optionally independently substituted with one to two oxo groups, nitrile, phenyl or one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms;

Z is:

aryl, heteroaryl selected from pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl and pyranyl, heterocycle selected from tetrahydropyrimidonyl, cyclohexanonyl, cyclohexanolyl, 2-oxa- or 2-thia-5-aza-bicyclo[2.2.1]heptanyl, pentamethylene sulfidyl, pentamethylene sulfoxidyl, pentamethylene sulfonyl, tetramethylene sulfidyl, tetramethylene sulfoxidyl or tetramethylene sulfonyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanonyl, 1,3-dioxanonyl, 1,4-dioxanyl, morpholino, thiomorpholino, thiomorpholino sulfoxidyl, thiomorpholino sulfonyl, piperidinyl, piperidinonyl, pyrrolidinyl and dioxolanyl,
each of the aforementioned Z are optionally substituted with one to three halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-3} alkoxy-C_{1-3} alkyl, C_{1-6} alkoxycarbonyl, aroyl, C_{1-3}acyl, oxo, hydroxy, pyridinyl-C_{1-3} alkyl, imidazolyl-C_{1-3} alkyl, tetrahydrofuranyl-C_{1-3} alkyl, nitrile-C_{1-3} alkyl, nitrile, carboxy, phenyl wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino, C_{1-6} alkyl-$S(O)_m$, or phenyl-$S(O)_m$ wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy, halogen or mono- or di-(C_{1-3} alkyl)amino;

or Z is optionally substituted with one to three amino or amino-C_{1-3} alkyl wherein the N atom is optionally independently mono- or di-substituted by aminoC_{1-6}alkyl, C_{1-3}alkyl, arylC_{0-3}alkyl, C_{1-5} alkoxyC_{1-3} alkyl, C_{1-5} alkoxy, aroyl, C_{1-3}acyl, C_{1-3}alkyl-$S(O)_m$- or arylC_{0-3}alkyl-$S(O)_m$- each of the aforementioned alkyl and aryl attached to the amino group is optionally substituted with one to two halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

or Z is optionally substituted with one to three aryl, heterocycle or heteroaryl as hereinabove described in this paragraph each in turn is optionally substituted by halogen, C_{1-6} alkyl or C_{1-6} alkoxy;

or Z is hydroxy, halogen, nitrile, amino wherein the N atom is optionally independently mono- or di-substituted by C_{1-3}acyl, C_{1-6}alkyl or C_{1-3}alkoxyC_{1-3}alkyl, C_{1-6}alkyl branched or unbranched, C_{1-6}alkoxy,

C_{1-3}acylamino, nitrileC_{1-4}alkyl, C_{1-6} alkyl-$S(O)_m$, and phenyl-$S(O)_m$, wherein the phenyl ring is optionally substituted with one to two halogen, C_{1-6} alkoxy, hydroxy or mono- or di-(C_{1-3} alkyl)amino;

each R_1 is independently:

C_{1-10} alkyl branched or unbranched optionally partially or fully halogenated, wherein one or more C atoms are optionally independently replaced by O, N or $S(O)_m$, and wherein said C_{1-10} alkyl is optionally substituted with one to three C_{3-10} cycloalkyl, hydroxy, oxo, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thienyl, furyl, dioxolanyl, isoxazolyl or isothiazolyl; each of the aforementioned being optionally substituted with one to five groups selected from halogen, C_{1-6} alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkanyl, C_{5-8} cycloalkenyl, hydroxy, nitrile, C_{1-3} alkoxy which is optionally partially or fully halogenated or $NH_2C(O)$, mono- or di(C_{1-3}alkyl)amino, and mono- or di(C_{1-3}alkyl)aminocarbonyl;

or R_1 is

cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC_{1-3}alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, $S(O)_m$, CHOH, >C=O, >C=S or NH;

phenyloxy or benzyloxy each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups optionally partially or fully halogenated, nitrile, hydroxyC_{1-3}alkyl or aryl; or an analog of such cycloaryl group wherein one to two ring methyne groups are independently replaced by N;

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl optionally

partially or fully halogenated, nitrile, hydroxyC_{1-3}alkyl or aryl; or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, $S(O)_m$, CHOH, >C=O, >C=S or NH;

C_{3-10} branched or unbranced alkenyl each being optionally partially or fully halogenated, and optionally substituted with one to three C_{1-5} branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl or isothiazolyl, each of the aforementioned being substituted with one to five halogen, C_{1-6} alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, hydroxy, nitrile, C_{1-3} alkyloxy which is optionally partially or fully halogenated, $NH_2C(O)$, mono- or di(C_{1-3}alkyl)aminocarbonyl; the C_{3-10} branched or unbranced alkenyl being optionally interrupted by one or more heteroatoms chosen from O, N and $S(O)_m$;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

oxo, nitrile, halogen;

silyl containing three C_{1-4} alkyl groups optionally partially or fully halogenated; or

C_{3-6} alkynyl branched or unbranched carbon chain optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH or $S(O)_m$ and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, hydroxy, pyrroldinyl, pyrrolyl, tetrahydropyranyl, one or more C_{1-4} alkyl optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C_{1-3}alkyl)amino optionally substituted by one

or more halogen atoms;

each R_2, R_4, and R_5 is

a C_{1-6} branched or unbranched alkyl optionally partially or fully halogenated, C_{1-6}acyl, aroyl, C_{1-4} branched or unbranched alkoxy, each being optionally partially or fully halogenated, halogen, methoxycarbonyl, C_{1-3} alkyl-$S(O)_m$ optionally partially or fully halogenated, or phenyl-$S(O)_m$;

OR_6, C_{1-6} alkoxy, hydroxy, nitrile, nitro, halogen;

or amino-$S(O)_m$- wherein the N atom is optionally independently mono- or di-substituted by C_{1-6}alkyl or arylC_{0-3}alkyl, or amino wherein the N atom is optionally independently mono- or di-substituted by C_{1-3}alkyl, arylC_{0-3}alkyl, C_{1-6}acyl, C_{1-6}alkyl-$S(O)_m$- or arylC_{0-3}alkyl-$S(O)_m$-, each of the aforementioned alkyl and aryl in this subparagraph are optionally partially or fully halogenated and optionally substituted with one to two C_{1-6} alkyl or C_{1-6} alkoxy;

each R_3 is independently:

phenyl, naphthyl, morpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, thiazolyl, oxazoyl, [1,3,4]oxadiazol, triazolyl, tetrazolyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl or indazolyl, each of the aforementioned is optionally substituted with one to three phenyl, naphthyl, heterocycle or heteroaryl as hereinabove described in this paragraph, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halogen, hydroxy, oxo, nitrile, C_{1-3} alkoxy optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocyclicoxy wherein

the heterocyclic or heteroaryl moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3}alky)lamino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl heterocyclic moiety is as hereinabove described in this paragraph, $NH_2C(O)$, a mono- or di-(C_{1-3}alkyl) aminocarbonyl, C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-5}alkyl)amino, mono- or di-(C_{1-3}alkyl)amino-C_{1-5} alkyl, amino-$S(O)_2$, di-(C_{1-3}alkyl)amino-$S(O)_2$, R_7-C_{1-5} alkyl, R_8-C_{1-5} alkoxy, R_9-C(O)-C_{1-5} alkyl, R_{10}-C_{1-5} alkyl(R_{11})N, carboxy-mono- or di-(C_{1-5}alkyl)-amino;

a fused aryl selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heteroaryl selected from cyclopentenopyridinyl, cyclohexanopyridinyl, cyclopentanopyrimidinyl, cyclohexanopyrimidinyl, cyclopentanopyrazinyl, cyclohexanopyrazinyl, cyclopentanopyridazinyl, cyclohexanopyridazinyl, cyclopentanoquinolinyl, cyclohexanoquinolinyl, cyclopentanoisoquinolinyl, cyclohexanoisoquinolinyl, cyclopentanoindolyl, cyclohexanoindolyl, cyclopentanobenzimidazolyl, cyclohexanobenzimidazolyl, cyclopentanobenzoxazolyl, cyclohexanobenzoxazolyl, cyclopentanoimidazolyl, cyclohexanoimidazolyl, cyclopentanothienyl and cyclohexanothienyl; wherein the fused aryl or fused heteroaryl ring is independently substituted with zero to three phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, C_{1-6} alkyl which is optionally partially or fully halogenated, halogen, nitrile, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy or heterocyclicoxy wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, nitro, amino, mono- or di-(C_{1-3}alkyl)amino, phenylamino, naphthylamino, heteroaryl or heterocyclic amino wherein the heteroaryl or heterocyclic moiety is as hereinabove described in this paragraph, $NH_2C(O)$, mono- or di-(C_{1-3}alkyl)aminocarbonyl, C_{1-4} alkyl-OC(O), C_{1-5} alkyl-C(O)-C_{1-4} alkyl, amino-C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino-C_{1-5} alkyl, R_{12}-C_{1-5} alkyl, R_{13}-C_{1-5} alkoxy, R_{14}-C(O)-C_{1-5} alkyl or R_{15}-C_{1-5} alkyl(R_{16})N;

cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl or bicycloheptanyl, each being optionally be partially or fully halogenated and optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are independently replaced by O, S, CHOH, >C=O, >C=S or NH;

cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl or bicycloheptenyl, each optionally substituted with one to three C_{1-3} alkyl groups;

C_{1-4} alkyl-phenyl-C(O)-C_{1-4} alkyl-, C_{1-4} alkyl-C(O)-C_{1-4} alkyl- or C_{1-4} alkyl-phenyl-$S(O)_m$-C_{1-4} alkyl-;

C_{1-6} alkyl or C_{1-6} branched or unbranched alkoxy each of which is optionally partially or fully halogenated or optionally substituted with R_{17};

OR_{18} or C_{1-6} alkyl optionally substituted with OR_{18};

amino or mono- or di-(C_{1-5}alkyl)amino optionally substituted with R_{19};

$R_{20}C(O)N(R_{21})$-, $R_{22}O$- or $R_{23}R_{24}NC(O)$-; $R_{26}(CH_2)_mC(O)N(R_{21})$-, $R_{23}R_{24}NC(O)$-C_{1-3}alkoxy or $R_{26}C(O)(CH_2)_mN(R_{21})$-;

C_{2-6}alkenyl substituted by $R_{23}R_{24}NC(O)$-;

C_{2-6} alkynyl branched or unbranched carbon chain, optionally partially or fully halogenated, wherein one or more methylene groups are optionally replaced by O, NH, $S(O)_m$ and wherein said alkynyl group is optionally independently substituted with one to two oxo groups, pyrroldinyl, pyrrolyl, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl one or more C_{1-4} alkyl

optionally substituted by one or more halogen atoms, nitrile, morpholino, piperidinyl, piperazinyl, imidazolyl, phenyl, pyridinyl, tetrazolyl, or mono- or di(C_{1-4} alkyl)amino optionally substituted by one or more halogen atoms;

C_{1-6}acyl or aroyl;

R_6 is a:

C_{1-4} alkyl optionally partially or fully halogenated and optionally substituted with R_{26};

each R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}, R_{15}, R_{17}, R_{19}, R_{25} and R_{26} is independently:

nitrile, phenyl, morpholino, piperidinyl, piperazinyl, imidazolyl, pyridinyl, tetrazolyl, amino or mono- or di-(C_{1-4}alkyl)amino optionally partially or fully halogenated;

each R_{11} and R_{16} is independently:

hydrogen or C_{1-4} alkyl optionally partially or fully halogenated;

R_{18} is independently:

hydrogen or a C_{1-4} alkyl optionally independently substituted with oxo or R_{25};

R_{20} is independently:

C_{1-10} alkyl optionally partially or fully halogenated, phenyl, or pyridinyl;

R_{21} is independently:

hydrogen or C_{1-3} alkyl optionally partially or fully halogenated;

each R_{22}, R_{23} and R_{24} is independently:

hydrogen, C_{1-6} alkyl optionally partially or fully halogenated, said C_{1-6} alkyl is optionally interrupted by one or more O, N or S, said C_{1-6} alkyl also being independently optionally substituted by mono- or di-(C_{1-3}alkyl)aminocarbonyl,

phenyl, pyridinyl, amino or mono- or di-(C_{1-4}alkyl)amino each of which is optionally partially or fully halogenated and optionally substituted with mono- or di-(C_{1-3}alkyl)amino;

or R_{23} and R_{24} taken together optionally form a heterocyclic or heteroaryl ring;

m = 0, 1 or 2;
W is O or S and
pharmaceutically acceptable derivatives thereof.

15) The Pharmaceutical composition according to claim 1, wherein the weight ratios of **A** to **B** are in the range from 1:300 to 20:1.

16) The Pharmaceutical composition according to claim 1 wherein the weight ratios of **A** to **B** are in the range from 1:200 to 10:1.

17) The Pharmaceutical composition according to claim 1, wherein a single application corresponds to a dosage of the active substance combination **A** and **B** of about 100 to 10000 μg.

18) The Pharmaceutical composition according to claim 15, wherein a single application corresponds to a dosage of the active substance combination **A** and **B** of about 1000 to 9000 μg.

19) The Pharmaceutical composition according to claim 1, wherein it is present in the form of a formulation suitable for inhalation.

20) The Pharmaceutical composition according to claim 19, wherein it is a formulation selected from among inhalable powders, propellant-containing metering aerosols and propellant-free inhalable solutions or suspensions.

21) The Pharmaceutical composition according to claim 20, wherein it is an inhalable powder which contains **A** and **B** in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.

22) The Inhalable powder according to claim 21, wherein the excipient has a maximum average particle size of up to 250μm, preferably between 10 and 150μm.

23) The Pharmaceutical composition according to claim 20, wherein it is an inhalable powder which contains only the active substances **A** and **B** as its ingredients.

24) A Capsule, wherein the capsule contains an inhalable powder according to claim 22.

25) The Pharmaceutical composition according to claim 20, wherein it is a propellant-containing inhalable aerosol which contains **A** and **B** in dissolved or dispersed form.

26) The Pharmaceutical composition according to claim 20, wherein it is a propellant-free inhalable solution or suspension which contains water, ethanol or a mixture of water and ethanol as solvent.

27) A method of treating an inflammatory or obstructive disease of the respiratory tract comprising administering to a patient in need thereof a therapeutically effective amount of a composition according to claim 1 .